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ASSISTANT VICE PRESIDENT
SCIENTIFIC AND REGULATORY AFFAIRS

PhRMA

February 7, 2000

Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: PhRMA Comments on Draft Guidance for Industry Entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*".

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $26 billion in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

General Comments:

(1) The hepatic guidance is very rigorous and would require studies for most drugs in development. Intense pharmacokinetic studies are extremely difficult to conduct in patients with significant hepatic impairment because of recruitment and logistical issues. These patients are fragile, have unstable disease, short life expectancies, and often are unwilling to undergo the rigors of clinical trials (multiple venipunctures and the need for confinement to a clinic for repeated-dose studies). Therefore, such studies should only be required for drugs likely to be used frequently in patients with hepatic disease, those with narrow therapeutic indices, and when a substantial amount of drug is metabolized by the liver. For drugs being developed for the treatment of hepatic disease or for use in populations where it is prevalent, adequate pharmacokinetic and pharmacodynamic information can be obtained from phase 2/3 clinical trials. For other drugs (except those with very steep dose-response curves), the 20% metabolism cutoff suggested in the draft guidance seems overly conservative. Fifty percent (50%) is considered to be a more appropriate number.

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(2) Considering the modest size of these studies and large intersubject variability among subjects with Child's Class A and B cirrhosis, it seems unlikely that a confidence interval approach will ever justify the conclusion "hepatic impairment has no impact on drug pharmacokinetics and, therefore, dose adjustment is not required." It would be helpful to discuss how clinical judgement/criteria can be used to support dosing recommendations and drug labeling.

(3) The guidance does not address drugs frequently used in patients with cancer and metastatic liver disease. In this common situation, cholestasis is often present in the absence of significant hepatocellular dysfunction (as reflected by the Child Pugh System). This situation would be particularly important for drugs excreted in bile and should be discussed in the guidance.

(4) Inclusion of patients with severe hepatic impairment (Child's C) in these studies (except in unusual circumstances) is probably not reasonable even when conducting a full study design. These patients have limited ability to give informed consent, are extremely ill/fragile, and data generated can probably not be extrapolated to the 'general population' because of marked variability among patients (eg, because of large differences in amounts of peripheral edema and/or massive ascites).

(5) Even in the absence of formal studies in patients with hepatic impairment, mass balance and drug interaction studies in healthy volunteers, in conjunction with preclinical information about drug metabolism, may be useful to include in labeling. This information could assist physicians who may choose to treat such patients with prescription medicines.

Specific Comments:

- Section **IIIA**, "**When Studies May Be Important**"

  (a) Include "for drugs likely to be used frequently in patients with hepatic impairment."
  (b) Define "substantial portion." Twenty percent, as discussed previously, seems to be unnecessarily conservative. PhRMA recommends that a value of 50% be used.

(b) Discussion of patients with renal failure who also develop significant hepatic dysfunction seems inappropriate. These are extremely ill patients
(c) with a typical life expectancy of days; therefore, it does not seem reasonable to address this situation in this guidance.
(d) Prodrugs that are converted by hepatic metabolism to pharmacologically active moieties should be discussed here.

- Section **IIIB**, "**When Studies May Not Be Important**"

(a) Drugs not metabolized by the liver (less than 50%). This would include compounds that are primarily creted unchanged in urine or those eliminated via the lungs (eg.. gaseous anesthetics).
(b) Drugs with very flat/broad dose response curves for safety and efficacy.

- Section **IV**, "**STUDY CONSIDERATIONS**"

(a) PhRMA recommends that FDA consider adding material similar to that in the Renal Guidance Document.

- Section **IVA1**, "**Reduced Study Design**, *Study Participants*"
  (a) Ensure consistency of nomenclature throughout the document (for example, see this section and appendix); PhRMA recommends: Child's A (mild impairment), Child's B (moderate impairment), and Child's C (severe impairment).
  (b) This design compares PK/PD in patients with Child's B (moderate) impairment to that of controls.
  (c) Due to the difficulty of matching control patients to patients with cirrhosis, PhRMA recommends that, in general, the control group be comprised of matched healthy subjects (those <u>without</u> the disease).

- Section **IVA2**, "**Reduced Study Design**, *Drug Administration*"
  (a) PhRMA recommends that pharmacokinetic assessment on day 1 of a multiple-dose study is not necessary. It makes these studies harder to complete and would provide little additional useful information. Steady-state pharmacokinetic information should adequately enable dosage adjustment.

- Section **IVA3**, " **Reduced Study Design**, *Sample Collection and Analysis*"
  (a) Protein binding should be determined for all highly bound drugs. Such information would allow appropriate interpretation of free and total drug

  concentrations/pharmacokinetic parameters regardless of drug extraction characteristics.

- Section **IVB**, "**Basic *Full* Study Design**"
  (a) PhRMA recommends that the basis full study design should be restricted to Child's A and B (mild and moderate). See "**General Comments.**"

- Section **VA**, "**DATA ANALYSIS, Parameter Estimation**"
  (a) Volumes of distribution (for oral drugs) would be Vd_Z/F and Vd_{SS}/F.

- Section **VC**, "**DATA ANALYSIS, Development of Dosing Recommendations**"
  (a) Clarify what is obvious; eg. twofold or greater increase **in AUC values**.
  (b) As stated in the guidance it will be nearly impossible to meet bioequivalence boundaries. This is due to small sample size, lack of crossover design, and high expected intersubject variability. Findings should be placed in clinical context (see previous **General Comments**). It would be useful to discuss how this could be done. Otherwise most labels for drugs studied in patients with hepatic impairment will be similar *regardless* of the data. For example, pharmacokinetic parameters will be presented and a statement such as "the drug should be used cautiously in patients with hepatic dysfunction if potential benefit outweighs risk" will be included.
  (c) Discussion of individual bioequivalence issues in this document, particularly considering the issues above, seems inappropriate. The entire paragraph is unhelpful and should be deleted.

- Section **VI**, "**LABELING**"
  (a) Considering the comments in section **VC**, it is unlikely that a recommendation of "no dosage modification" will be possible.
  (b) Rather than contraindicate a drug in patients with severe hepatic dysfunction (Child's C) when data are not available, PhRMA recommends that FDA consider "data is not available in patients with severe hepatic disease. The drug should be used with great caution only when the potential benefit outweighs the risk."

- Section **VIA**2b(i and ii), "**LABELING, Clinical Pharmacology Section,** *Special Populations,* Limited **hepatic** elimination, Wide and Narrow TI"
  (a) The renal failure and hepatic impairment discussion in both sections should be deleted (see previous discussion section **IIIA**).

- Section **VIA**2ci, " **LABELING, Clinical Pharmacology Section,** *Special Populations,* Extensive hepatic elimination, Wide and Narrow TI"
  (a) The absence of data for a wide TI drug probably should not lead to the statement "Patients with impaired liver function would require reduced initial and ..."

PhRMA urges FDA to continue the scientific development, but postpone the issuance of a guidance until that development occurs and a consensus develops.

PhRMA appreciates the opportunity to provide comments on this important draft guidance.

Sincerely,

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COMMENTS: